

Acute Coronary Syndromes

Rebound Thrombin Generation After Heparin Therapy in Unstable Angina

A Randomized Comparison Between Unfractionated and Low-Molecular-Weight Heparin

Nick R. Bijsterveld, MD,* Arno H. Moons, MD,* Joost C. M. Meijers, PhD,† Jan G. P. Tijssen, PhD,* Harry R. Büller, MD, PhD,† Marcel Levi, MD, PhD,† Ron J. G. Peters, MD, PhD*

Amsterdam, Netherlands

OBJECTIVES	This study compared rebound coagulation in patients with acute coronary syndrome patients after discontinuation of unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH).
BACKGROUND	Up to a quarter of patients hospitalized for unstable angina experience recurrent ischemia after discontinuation of UFH or LMWH therapy, which may be the result of rebound coagulation activation and subsequent thrombosis. It is unknown whether UFH and LMWH differ in this respect.
METHODS	We randomized 71 patients admitted with unstable angina to intravenous UFH or subcutaneous LMWH (dalteparin) and measured plasma markers of coagulation before, during, and after treatment.
RESULTS	A complete series of measurements was obtained in 59 patients. Plasma prothrombin fragment 1+2 (F_{1+2}) levels decreased in both groups during treatment. After loss of therapeutic plasma drug levels, F_{1+2} increased (within 3 h) to a maximum level at 12 to 24 h that was higher than before or during treatment in both groups ($p < 0.0001$). In both groups, F_{1+2} levels remained higher than pretreatment up to 24 h after discontinuation. Similarly, thrombin-antithrombin (TAT) levels exceeded treatment and pretreatment levels, at a slower rate after dalteparin than after UFH. However, after dalteparin a higher peak value of TAT was observed.
CONCLUSIONS	Rebound coagulation activation occurs within hours after discontinuation of both UFH and dalteparin. With both drugs, thrombin generation is significantly greater after treatment than before or during treatment. A longer duration or weaning of treatment, or continuation with another anticoagulant treatment, may reduce rebound coagulation activation and ischemic events. (J Am Coll Cardiol 2002;39:811-7) © 2002 by the American College of Cardiology Foundation

The medical treatment of patients with non-ST-segment elevation acute coronary syndromes (ACS) includes short-term intensive anticoagulant treatment for prevention of thrombotic occlusion of the culprit coronary artery. Both unfractionated heparin (UFH) and low-molecular-weight heparin (LMWH) treatment result in a 60% reduction of death or myocardial infarction during hospitalization as compared to placebo (1-6). However, approximately 25% of patients with ACS suffer from recurrent ischemic events (death, infarction or need for urgent revascularization) during the first 30 days after hospital admission (1-4). Several studies indicate clustering of these events shortly after cessation of UFH (7-11). In the Global Utilization of Streptokinase and tPA for Occluded Arteries (GUSTO I) study (7), including patients with acute myocardial infar-

tion, a marked clustering of reinfarctions was observed within hours after discontinuation of UFH infusion. Clinical evidence of rebound ischemia in patients with unstable angina was first described by Theroux et al. (8). In a substudy of the Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-wave Coronary Events (ESSENCE) trial (12), patients with ACS randomized to UFH or enoxaparin treatment were monitored by continuous ST-segment registration during the first 48 h on treatment and the first 48 h after treatment. Treatment discontinuation resulted in a significant increase of ischemic episodes in both groups.

A plausible cause of these recurrent ischemic events after cessation of heparin is reactivation of the coagulation system. With the loss of therapeutic heparin levels, prothrombotic factors such as thrombin and tissue factor in the culprit lesion of the coronary artery could reactivate the coagulation system, rapidly resulting in thrombus growth as well as platelet recruitment with subsequent ischemia.

If rebound coagulation is responsible for recurrent ischemic events after UFH discontinuation, the more gradual plasma clearance of LMWH in comparison with UFH

From the Departments of *Cardiology and †Vascular Medicine, Academic Medical Center, Amsterdam, Netherlands. This study was supported by Pharmacia B. V., Netherlands. Dr. Meijers is an established investigator of the Netherlands Heart Foundation (Grant D96.022).

Manuscript received July 11, 2001; revised manuscript received November 14, 2001, accepted December 3, 2001.

Abbreviations and Acronyms

ACS	= acute coronary syndromes
APC	= activated protein C
CK-MB	= creatinine kinase-MB
ECG	= electrocardiogram
F ₁₊₂	= prothrombin fragment 1+2
IV	= intravenous
LMWH	= low-molecular-weight heparin
PAP	= plasmin-antiplasmin complexes
TAT	= thrombin-antithrombin complexes
TFPI	= tissue factor pathway inhibitor
UFH	= unfractionated heparin

might avoid or reduce this phenomenon. Clinically superior results of LMWH over UFH in patients with ACS could partially be based on such a difference (1-4). To date, a rebound phenomenon has not been reported for LMWH.

Therefore, we performed a randomized study to determine whether rebound activation of coagulation occurs after cessation of LMWH treatment, and whether this is different from rebound phenomenon seen with UFH.

METHODS

Patient selection. Consecutive patients admitted to our coronary care unit for non-ST-segment elevation ACS were screened for eligibility. Inclusion criteria were rest angina of at least 5 min in duration and either electrocardiogram (ECG) changes compatible with acute ischemia (ST-segment depression ≥ 0.1 mV in ≥ 2 contiguous leads, T-wave inversion ≥ 0.1 mV, transient ST elevation or new left bundle branch block), creatinine kinase-MB (CK-MB) levels of at least twice the normal limit or a history of documented coronary artery disease. Excluded were patients with known coagulation disorders, using anticoagulant agents or scheduled to be transferred before the end of the study.

Informed consent was obtained from all patients. Randomization was performed with sealed envelopes containing treatment allocation. The study was approved by the Institutional Review Board of the Academic Medical Center in Amsterdam.

Treatment. Unfractionated heparin treatment started with an intravenous (IV) bolus of 5,000 U, followed by continuous infusion to reach a partial thromboplastin time between 60 and 90 s (i.e., 2- to 2.5-fold increase of control value). Low-molecular-weight heparin treatment consisted of twice daily subcutaneous injections 120 IU/kg dalteparin (Fragmin). All patients received aspirin 100 mg daily. By protocol, patients were treated with study medication until clinically stable, for at least 48 h from onset of treatment or, if applicable, at least 48 h after catheterization.

Additional medication was left to the discretion of the treating physician, but included beta-blockers and IV nitroglycerin. Patients underwent coronary angiography only if they developed severe refractory ischemia.

Blood sampling. Blood samples were collected before start of study medication, during steady-state anticoagulation (24 h after start of study medication) and at 0, 3, 6, 12, 24 and 48 h after loss of therapeutic levels of the respective heparins. For patients treated with UFH, cessation of treatment was defined as time of discontinuation of the infusion. For patients treated with dalteparin, cessation of treatment was defined as 12 h after the last subcutaneous injection (Fig. 1).

Blood samples were obtained through an IV infusion system that was distal to other systems and not used for medication. At each sampling, the first 2 ml of blood was discarded and 10 ml was collected in citrated Vacutainer tubes (4.5 ml citrate sodium -0.105 M siliconated 1 to 10). Blood was centrifuged at 3,000 rpm for 20 min at 6°C. Plasma was separated, pooled and filled out in cryocups and

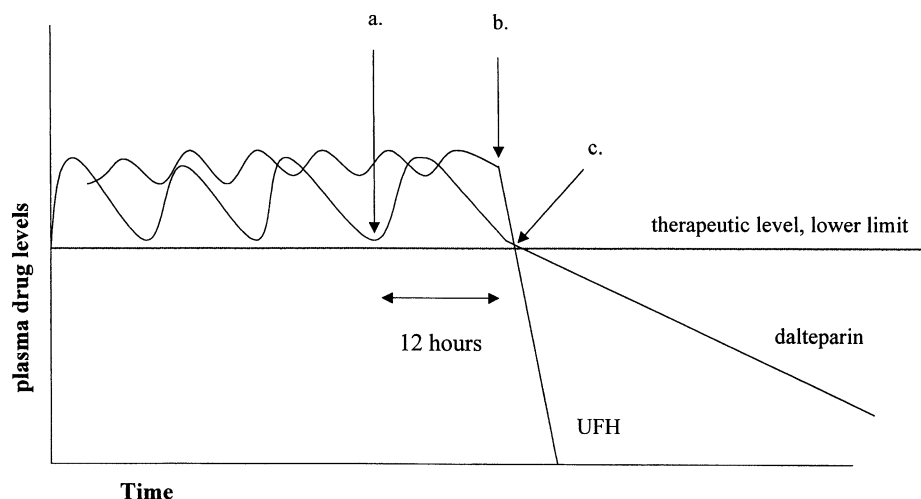


Figure 1. Schematic anticoagulation levels of unfractionated heparin (UFH) and low-molecular-weight heparin and definition of discontinuation time point for UFH and dalteparin. (a) last dose of dalteparin; (b) cessation of UFH, discontinuation time point; (c) discontinuation time point for dalteparin.

frozen at -80°C until analysis was performed. These procedures were completed within 1 h after blood sampling. **Assays.** Quantification of prothrombin fragment 1+2 (F_{1+2}), thrombin-antithrombin complexes (TAT) and plasmin-antiplasmin complexes (PAP) was performed by sandwich-type enzyme-linked immunosorbent assays (Dade-Behring, Marburg, Germany). Upper normal values of these markers were F_{1+2} 1.6 nmol/l, TAT 4.6 $\mu\text{g/l}$ and PAP 700 $\mu\text{g/l}$.

Levels of heparin activity were determined by a microtiterplate chromogenic anti-factor Xa activity assay (Chromogenix) and calibrated against UFH or dalteparin.

Clinical outcome. Recurrent ischemic events during hospitalization were classified as angina with ischemic ECG changes, angina leading to angiography or revascularization, reinfarction with CK-MB rise of at least twice the normal limit and death.

Statistical analysis. To determine differences between time points within a treatment group, a nonparametric related samples test (Wilcoxon) was performed for each of the eight time points relative to the preceding time point. For comparisons between the UFH and dalteparin groups, a nonparametric independent samples test (Mann-Whitney U test) was calculated. All statistical analyses were performed with SPSS 10.0.7 (Chicago, Illinois). To examine the absolute change of a parameter after treatment cessation, stop values were subtracted from the following values and were analyzed using a nonparametric independent samples test (Mann-Whitney U test).

No formal repeated measurement analyses could be performed because the data were not normally distributed.

Patients were excluded from the analysis when more than two blood samples were missing, unless this was due to the occurrence of a recurrent ischemic event resulting in therapeutic intervention (angioplasty, restart of anticoagulation).

Highly elevated levels of F_{1+2} , TAT and PAP were considered as sampling errors with ex-vivo coagulation activation and excluded from the analysis. Cut-off values for F_{1+2} were 8 nmol/l; TAT 50 $\mu\text{g/l}$ and PAP 1,000 $\mu\text{g/l}$. This resulted in the exclusion of 1%, 6% and 6% of the total F_{1+2} , TAT and PAP samples, respectively.

RESULTS

Of 71 study patients, 38 were randomized to UFH and 33 to dalteparin. Twelve patients were not included in the analysis because they had more than two missing blood samples. The reasons for incomplete blood sampling were transfer to other hospitals ($n = 4$), continuation of open-label UFH or LMWH due to angioplasty or planned coronary artery bypass graft ($n = 6$), at patient's request ($n = 1$) or at doctor's request ($n = 1$).

Table 1 summarizes baseline characteristics of the 59 included patients. No significant differences between the UFH and dalteparin groups were observed. Median duration of treatment from first through the last dose was 48 h

Table 1. Baseline Characteristics

	UFH n (%)	Dalteparin n (%)
Female/male	9/20	14/16
Age (yrs)	63	61
Weight (mean in kg)	83	78
Diabetes	7 (24)	7 (23)
Smoking	13 (45)	11 (37)
Previous hyperlipidemia	6 (21)	13 (43)
Previous hypertension	11 (38)	13 (43)
Previous stable angina	10 (34)	16 (53)
Previous unstable angina	9 (31)	14 (47)
Previous myocardial infarction	7 (24)	13 (43)
Previous angioplasty	6 (21)	12 (40)
Previous CABG	2 (7)	3 (10)
Previous aspirin use	14 (50)	21 (70)
Angioplasty during heparin treatment	6 (21)	7 (23)
Median administration of anticoagulant treatment (h)	48	55

CABG = coronary artery bypass graft; UFH = unfractionated heparin.

for UFH patients and 55 h for dalteparin patients. Patients treated with UFH had median prothrombin times of 66 s at 24 h after start and 68 s immediately before discontinuation of therapy. While on anticoagulant treatment six UFH and seven dalteparin patients underwent coronary angioplasty, after which treatment was continued for a median of 44 h.

Thrombin generation. On admission, but before study medication was started, F_{1+2} plasma levels were comparable in both groups (Fig. 2). During the first 24 h of treatment, both UFH and dalteparin significantly decreased F_{1+2} levels ($p < 0.02$), although dalteparin resulted in a greater decrease compared to UFH ($p = 0.002$). At the end of the treatment period, F_{1+2} levels in the dalteparin group were not significantly different from those in the UFH (see time point "stop"). No significant changes of F_{1+2} were observed in the UFH group during the remaining treatment period.

In the UFH group, treatment cessation resulted in a rapid increase of F_{1+2} , from 0.74 nmol/l to 1.25 nmol/l 3 h after stopping ($p < 0.001$). This increase persisted through 6 and 12 h after stop and reached a maximum level of 1.48 nmol/L at 12 h. Dalteparin cessation also resulted in an increase of thrombin generation with similar time to peak levels at 12 h (1.21 nmol/l) after cessation. Compared to UFH, F_{1+2} levels were lower at 3 and 6 h after of dalteparin ($p = 0.002$ and $p = 0.02$, respectively) and remained lower although the 12, 24 and 48 h samples were not significantly different. At 48 h after treatment discontinuation, F_{1+2} levels in both groups were at a similar level. When we corrected for F_{1+2} measured at the stop time point, no differences in F_{1+2} generation between UFH and dalteparin were observed. Both groups revealed significant increases of F_{1+2} levels with a maximum increase of 0.52 nmol/l at 6 h in the UFH group and of 0.61 nmol/l at 12 h in the dalteparin group (both $p < 0.0001$ compared to stop values).

Compared to pretreatment levels, both groups showed increased F_{1+2} levels up to 24 h after treatment discontinuation ($p < 0.03$).

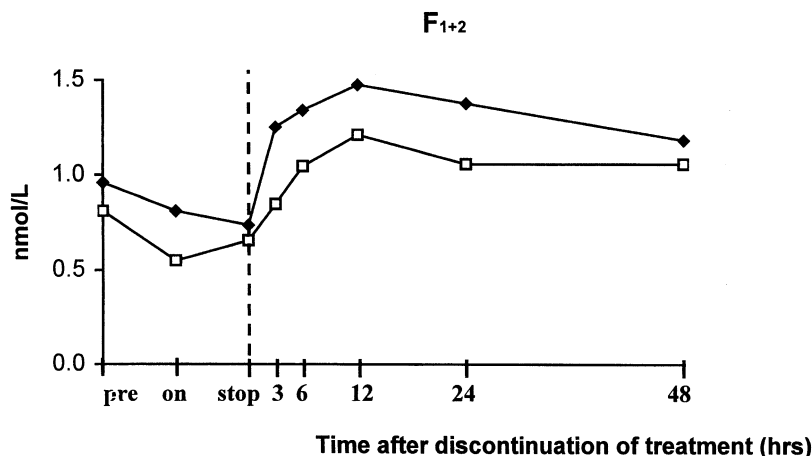


Figure 2. Median plasma levels of prothrombin fragment 1+2 (F_{1+2}) before, during, and after unfractionated heparin (UFH) and dalteparin treatment. **Black diamond** = UFH; **white square** = dalteparin. Samples were obtained before treatment start (**pre**), 24 h after start (**on**), at discontinuation of UFH or dalteparin treatment (**stop**) and at 3, 6, 12, 24 and 48 h after discontinuation of treatment (3, 6, 12, 24, 48, respectively). Interquartile range of the values at the various time points was 0.75 for UFH and 0.56 for dalteparin.

Thrombin-antithrombin complex formation. Figure 3 presents the median plasma levels of TAT in both groups. Pretreatment levels were comparable in both groups ($7.3 \mu\text{g/l}$ in UFH and $5.4 \mu\text{g/l}$ in dalteparin). Dalteparin treatment did not result in changes of TAT levels 24 h after treatment start, whereas UFH treatment resulted in a level increase from $7.3 \mu\text{g/l}$ to $13.8 \mu\text{g/l}$ ($p = 0.121$), which was significantly different between both groups ($p = 0.042$). Continuation of UFH treatment restored plasma TAT levels similar to those in the dalteparin group at 48 h after treatment start ($7.2 \mu\text{g/l}$ and $6.1 \mu\text{g/l}$, respectively, $p = 0.3$).

When treatment with UFH was stopped, a rapid increase of TAT levels was observed at 3 h, reaching a maximum at 6 h after discontinuation ($20.6 \mu\text{g/l}$). At 12, 24 and 48 h, TAT levels decreased to $13.5 \mu\text{g/l}$, $12.2 \mu\text{g/l}$ and $4.8 \mu\text{g/l}$, respectively. In the dalteparin group, a slight increase was

observed 3 h after treatment stop, with a steep increase at 6 and 12 h to TAT levels of $15.2 \mu\text{g/l}$ and $31.4 \mu\text{g/l}$, respectively. At 24 h, TAT levels were similar in both groups, and the 48 h levels were comparable with pretreatment levels. Differences between UFH and dalteparin were observed at 3 and 12 h after treatment stop ($p = 0.01$ and $p = 0.004$, respectively). When we corrected for TAT levels measured at the stop time point, only dalteparin differed from UFH at the 12-h post-treatment time point ($p = 0.01$).

Fibrinolysis. Plasmin-antiplasmin levels, an indicator of fibrinolytic system activity, are presented in Figure 4. Both UFH and dalteparin effectively suppressed the generation of PAP complexes, indicating a decrease in fibrinolysis during treatment ($p < 0.001$), which persisted until treatment discontinuation. Cessation resulted in both groups to marked and persistent increases of PAP levels that were still

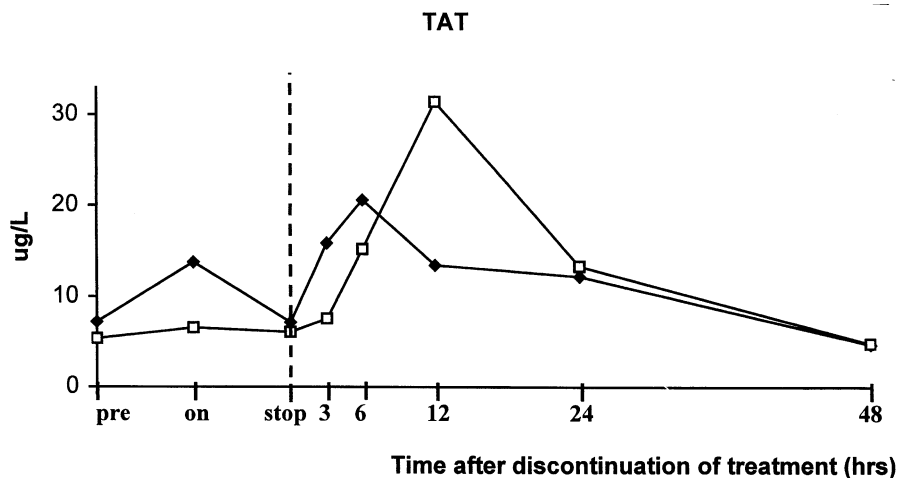


Figure 3. Median plasma levels of thrombin-antithrombin complexes (TAT) before, during, and after unfractionated heparin (UFH) and dalteparin treatment. **Black diamond** = UFH; **white square** = dalteparin. Samples were obtained before treatment start (**pre**), 24 h after start (**on**), at discontinuation of UFH or dalteparin treatment (**stop**) and at 3, 6, 12, 24 and 48 h after discontinuation of treatment (3, 6, 12, 24, 48, respectively). Interquartile range of the values at the various time points was 15.6 for UFH and 11.9 for dalteparin.

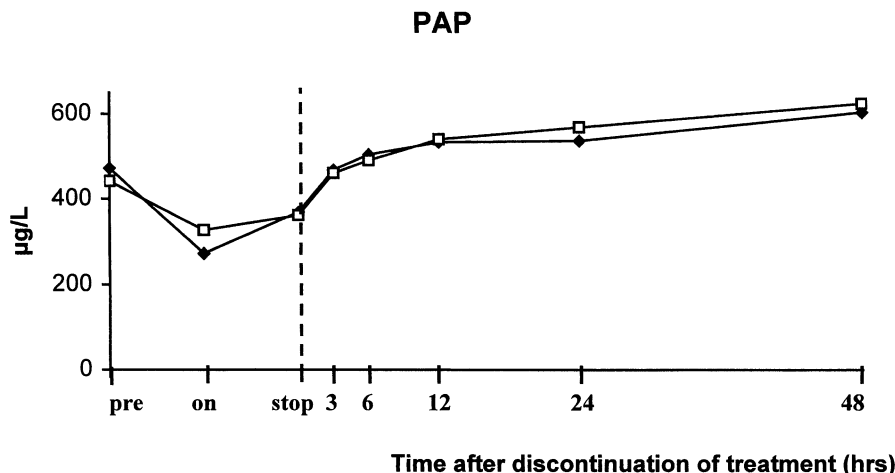


Figure 4. Median plasma levels of plasmin-antiplasmin (PAP) before, during, and after unfractionated heparin (UFH) and dalteparin treatment. **Black diamond** = UFH; **white square** = dalteparin. Samples were obtained before treatment start (**pre**), 24 h after start (**on**), at discontinuation of UFH or dalteparin treatment (**stop**) and at 3, 6, 12, 24 and 48 h after discontinuation of treatment (3, 6, 12, 24, 48, respectively). Interquartile range of the values at the various time points was 269.2 for UFH and 292.0 for dalteparin.

rising at 48 h and were significantly higher than pretreatment levels ($p < 0.02$).

Anti-Xa levels. Anti-Xa levels, an indicator for heparin activity, were measured at all time points and median values and are presented in Figure 5. There was a significant difference in anti-Xa levels during steady-state treatment between dalteparin (0.74 U/ml) and UFH (0.30 U/ml) treatment ($p = 0.004$). At treatment stop, anti-Xa levels were comparable, consistent with the assumption that 12 h after the last subcutaneous injection of dalteparin, therapeutic anticoagulation levels are still present. A more gradual decline in anti-Xa levels was observed in the dalteparin group, with anti-Xa levels at 3 and 6 h of 0.23 U/ml and 0.12 U/ml, respectively ($p < 0.0001$ and $p = 0.26$ compared to UFH, respectively). Anti-Xa was nearly undetectable in the UFH group 3 h after cessation of infusion (0.01 U/ml).

Clinical recurrent ischemic events. Seven patients experienced recurrent angina with ECG changes within 48 h after treatment cessation (three UFH and four dalteparin patients). All were event free during the treatment period. In three patients, anticoagulation therapy was restarted, and one urgent revascularization was performed. None of the patients died or experienced a myocardial infarction during the first 48 h after treatment, although one UFH patient died later during hospitalization. Four of these seven patients showed F_{1+2} increases above the upper limit of normal after discontinuation (>1.6 nmol/l, median peak level of 6.0 nmol/l) simultaneous or preceding it up to 6 h, whereas 28 patients without recurrent angina also showed increased F_{1+2} levels (median peak level of 2.2 nmol/l). Elevated TAT levels (>4.6 µg/l) after discontinuation were common in both groups (at least at one time point in all but

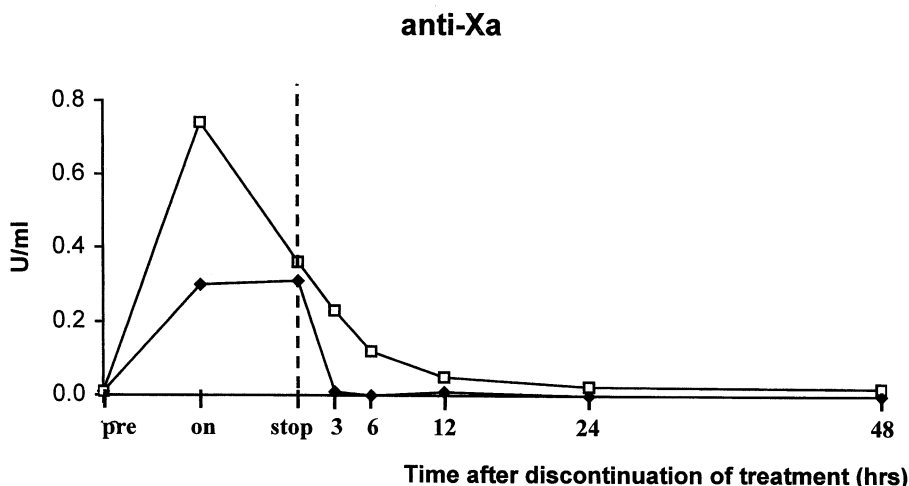


Figure 5. Median plasma levels of anti-factor Xa (anti-Xa) before, during, and after unfractionated heparin (UFH) and dalteparin treatment. **Black diamond** = UFH; **white square** = dalteparin. Samples were obtained before treatment start (**pre**), 24 h after start (**on**), at discontinuation of UFH or dalteparin treatment (**stop**) and at 3, 6, 12, 24 and 48 h after discontinuation of treatment (3, 6, 12, 24, 48, respectively).

one patient) and levels were similar in patients with and without recurrent angina (median level of 33.4 $\mu\text{g/l}$ and 31.7 $\mu\text{g/l}$, respectively).

DISCUSSION

This study demonstrates that rebound activation of the coagulation system occurs after discontinuation of both UFH and dalteparin treatment, and it is the first to compare the two. We found that the time course and the magnitude of this rebound phenomenon was not different for UFH and dalteparin. The peak level of F_{1+2} observed after discontinuation of dalteparin compared to UFH was similar after correction for stop F_{1+2} values, indicating similar absolute increases of F_{1+2} . After both treatments, a sharp increase in thrombin formation and TAT complexes was observed. This was also reflected in plasma PAP complexes, which increased up to 48 h after termination of heparin administration. Remarkably, levels of F_{1+2} and PAP remained elevated at least 24 h after treatment was discontinued, and these levels were significantly higher than levels before treatment was started, suggesting a heparin-induced elevation of these markers.

Differences between UFH and dalteparin were evident during treatment, when dalteparin was more effective in decreasing F_{1+2} levels. Thrombin-antithrombin levels were unaffected by dalteparin treatment, but in the UFH group a significant increase was observed. In both groups PAP levels decreased. The more effective suppression of F_{1+2} by dalteparin is consistent with the higher level of anti-Xa activity (Fig. 5). Stable UFH levels are usually not reached within 24 h, whereas dalteparin results in predictable levels immediately after treatment is started. This difference is likely reflected in the amount of F_{1+2} formed. Although one would expect TAT levels to show a similar pattern, no change was observed with dalteparin treatment, whereas UFH resulted in a rise of these complexes (Fig. 3). Although subtherapeutic levels of anticoagulation will fail to decrease TAT levels, this cannot explain the increase of the plasma levels as seen in the UFH group. Therefore, LMWH administration may affect TAT complex formation in a different way.

Our study was too small to detect clinical differences between the treatment groups. There was no clear relation between clinical recurrent angina and increases of F_{1+2} and TAT. However, peak levels of F_{1+2} were higher in patients with recurrent angina (6.0 nmol/l vs. 2.2 nmol/l), suggesting that the magnitude of thrombin generation may contribute to the recurrence of clinical ischemia.

Previous studies. Rebound thrombin generation after discontinuation of UFH has been investigated previously (13–15). In a study by Granger et al. (13), UFH cessation resulted in increases of both F_{1+2} and fibrinopeptide A at 3 to 6 h. Normalization of all markers to pretreatment levels was observed, whereas we observed that only TAT levels decreased to baseline values at 48 h after cessation. Becker et

al. (14) found increased thrombin generation as soon as 1 h after UFH cessation and further increasing at 24 h. Other studies have shown that coagulation parameters may remain elevated during the weeks or even months after the onset (and treatment) of ACS (16–18).

Thrombin generation observed after discontinuation of heparin is not likely explained by returning to the natural course of the disease. In a Fragmin and Fast Revascularisation during Instability in Coronary artery disease (FRISC) substudy, placebo-treated patients showed no significant changes in plasma F_{1+2} levels in the first five days after admission (16).

Potential mechanisms. A state of hypercoagulability after heparin treatment may be induced by tissue factor pathway inhibitor (TFPI) depletion (19). This lipoprotein, bound to endothelial cells, is a natural anticoagulant inhibiting both factor Xa as well as the tissue factor/fVIIa/fXa complex. Infusion of heparin releases TFPI from endothelial cells, and continued administration of heparin may result in depletion of this anticoagulant. We did not perform endothelium-bound TFPI measurements because UFH boluses are required for quantification of this protein. Second, both UFH and LMWH inhibit the generation of activated protein C (APC), resulting in low levels of this natural anticoagulant during treatment (20). Cessation of anticoagulation at low APC levels may promote rebound coagulation.

It is conceivable that angioplasty would stabilize the culprit lesion and thus prevent rebound phenomena. However, in our study, among 8 of 13 patients who underwent angioplasty during treatment, discontinuation of therapy resulted in an increase of F_{1+2} above 1.6 nmol/l, suggesting that the intervention may not result in a different rebound pattern.

Clinical implications. Rebound thrombotic phenomena have important clinical implications (7–11). Several clinical studies have investigated the effect of prolonged treatment with either LMWH (2,3,4,21) or oral anticoagulant treatment after ACS (22–24). In the FRISC II study, a subgroup of patients with ACS who continued dalteparin treatment up to 90 days after hospital discharge did not benefit from this regimen compared to short-term dalteparin (21). However, when high risk patients were selected on the basis of troponin T-levels and ST-segment shifts on admission, a significant reduction of death alone or death and myocardial infarction at 90 days was obtained (25). It is unclear if our findings with dalteparin can be extrapolated to other LMWHs. In clinical studies, differences in outcome have suggested that LMWHs are not equally effective (1–4,21). However, variations in the designs of the studies may explain these differences, and a direct comparison is lacking. There have been no observations on rebound coagulation after discontinuation of other LMWHs.

A recent publication focused on long-term oral anticoagulation in patients discharged after hospitalization for ACS (23). In patients compliant with the medication, oral

anticoagulants resulted in a reduction of the combined end point cardiac death, myocardial infarction or stroke (risk ratio 0.68, 95% confidence interval 0.48 to 0.95). Cessation of oral anticoagulation did not result in a rebound of ischemic events during one-month follow up.

Because aspirin has been shown to reduce rebound effects (8), additional inhibitors of platelet function may further reduce rebound thrombosis. However, of five patients in our study who received a thienopyridine because of stent implantation, two showed increases of F_{1+2} above normal limits after discontinuation of heparin treatment.

Summary. Treatment with both UFH and dalteparin is followed by reactivation of coagulation to levels higher than before or during treatment, and persisting at least 48 h after treatment discontinuation. In dalteparin-treated patients, reactivation peak levels were not different from those seen after discontinuation of UFH. Rebound thrombin generation in patients with unstable angina or myocardial infarction is likely the cause of clinical recurrent ischemia seen shortly after treatment cessation.

Reprint requests and correspondence: Dr. Ron J. G. Peters, Department of Cardiology, Room F3-236, Academic Medical Center, P.O. Box 22660, 1100 DD Amsterdam, Netherlands. E-mail: R.J.Peters@amc.uva.nl.

REFERENCES

- Cohen M, Demers C, Gurfinkel EP, et al. A comparison of low-molecular-weight heparin with unfractionated heparin for unstable coronary artery disease: Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events Study Group. *N Engl J Med* 1997;337:447-52.
- Klein W, Buchwald A, Hillis SE, et al. Comparison of low-molecular-weight heparin with unfractionated heparin acutely and with placebo for 6 weeks in the management of unstable coronary artery disease: Fragmin in unstable coronary artery disease study (FRIC). *Circulation* 1997;96:61-8.
- Anonymous. Comparison of two treatment durations (6 days and 14 days) of a low molecular weight heparin with a 6-day treatment of unfractionated heparin in the initial management of unstable angina or non-Q wave myocardial infarction: FRAXIS (FRAXiparine in Ischaemic Syndrome). *Eur Heart J* 1999;20:1553-62.
- Antman EM, McCabe CH, Gurfinkel EP, et al. Enoxaparin prevents death and cardiac ischemic events in unstable angina/non-Q-wave myocardial infarction: Results of the Thrombolysis In Myocardial Infarction (TIMI) 11B trial. *Circulation* 1999;100:1593-601.
- Anonymous. Low-molecular-weight heparin during instability in coronary artery disease: Fragmin during Instability in Coronary Artery Disease (FRISC) study. *Lancet* 1996;347:561-8.
- Eikelboom JW, Anand SS, Malmberg K, Weitz JI, Ginsberg JS, Yusuf S. Unfractionated heparin and low-molecular-weight heparin in acute coronary syndrome without ST elevation: a meta-analysis. *Lancet* 2000;355:1936-42.
- Granger CB, Hirsch J, Califf RM, et al. Activated partial thromboplastin time and outcome after thrombolytic therapy for acute myocardial infarction: results from the GUSTO-I trial. *Circulation* 1996;93:870-8.
- Theroux P, Waters D, Lam J, Juneau M, McCans J. Reactivation of unstable angina after the discontinuation of heparin. *N Engl J Med* 1992;327:141-5.
- Di Tano G, Mazzu A. Early reactivation of ischaemia after abrupt discontinuation of heparin in acute myocardial infarction. *Br Heart J* 1995;74:131-3.
- Gold HK, Torres FW, Garabedian HD, et al. Evidence for a rebound coagulation phenomenon after cessation of a 4-hour infusion of a specific thrombin inhibitor in patients with unstable angina pectoris. *J Am Coll Cardiol* 1993;21:1039-47.
- Bahit MC, Topol EJ, Califf RM, et al. Reactivation of ischemic events in acute coronary syndromes: results from GUSTO-IIb. Global use of strategies to open occluded arteries in acute coronary syndromes. *J Am Coll Cardiol* 2001;37:1001-7.
- Goodman SG, Barr A, Sobtchouk A, et al. Low molecular weight heparin decreases rebound ischemia in unstable angina or non-Q-wave myocardial infarction: the Canadian ESSENCE ST segment monitoring substudy. *J Am Coll Cardiol* 2000;36:1507-13.
- Granger CB, Miller JM, Bovill EG, et al. Rebound increase in thrombin generation and activity after cessation of intravenous heparin in patients with acute coronary syndromes. *Circulation* 1995;91:1929-35.
- Becker RC, Spencer FA, Li Y, et al. Thrombin generation after the abrupt cessation of intravenous unfractionated heparin among patients with acute coronary syndromes: potential mechanisms for heightened prothrombotic potential. *J Am Coll Cardiol* 1999;34:1020-7.
- Linder R, Oldgren J, Egberg N, et al. The effect of a low molecular mass thrombin inhibitor, inogatran, and heparin on thrombin generation and fibrin turnover in patients with unstable coronary artery disease. *Eur Heart J* 1999;20:506-18.
- Ernoffsson M, Strekerud F, Toss H, et al. Low-molecular weight heparin reduces the generation and activity of thrombin in unstable coronary artery disease. *Thromb Haemost* 1998;79:491-4.
- Flather MD, Weitz JI, Yusuf S, et al. Reactivation of coagulation after stopping infusions of recombinant hirudin and unfractionated heparin in unstable angina and myocardial infarction without ST elevation: results of a randomized trial. *Eur Heart J* 2000;21:1473-81.
- Merlini PA, Bauer KA, Oltrona L, et al. Persistent activation of coagulation mechanism in unstable angina and myocardial infarction. *Circulation* 1994;90:61-8.
- Hansen JB, Sandset PM. Differential effects of low molecular weight heparin and unfractionated heparin on circulating levels of antithrombin and tissue factor pathway inhibitor (TFPI): a possible mechanism for difference in therapeutic efficacy. *Thromb Res* 1998;91:177-81.
- Linder R, Blomback M, Egberg N, Grip L. Thrombin inhibitors suppress the thrombin-thrombomodulin-mediated generation of activated protein C. *Thromb Res* 1999;95:117-25.
- FRagmin and Fast Revascularisation during InStability in Coronary artery disease Investigators. Long-term low-molecular-mass heparin in unstable coronary-artery disease: FRISC II prospective randomised multicentre study. *Lancet* 1999;354:701-7.
- Anonymous. A double-blind trial to assess long-term oral anticoagulant therapy in elderly patients after myocardial infarction. Report of the Sixty Plus Reinfarction Study Research Group. *Lancet* 1980;2:989-94.
- The Organization to Assess Strategies for Ischemic Syndromes (OASIS) Investigators. Effects of long-term, moderate-intensity oral anticoagulation in addition to aspirin in unstable angina. *J Am Coll Cardiol* 2001;37:475-84.
- Anonymous. Aspirin plus medium intensity coumadin versus aspirin alone in the prevention of reocclusion after successful thrombolysis for suspected acute myocardial infarction: preliminary results of the APRICOT- 2 trial. Presented at the XXII European Society Congress; August 2000; Amsterdam.
- Lindahl B, Diderholm E, Lagerqvist B, Wallentin L. Effect on mortality by LMW heparin in relation to STT changes and level of troponin T in unstable coronary artery disease: a FRISC II substudy (abstr). *Circulation* 2000;102:591.